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(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: CRAWLEY, Graham, Charles [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: MACK, John, Richard; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

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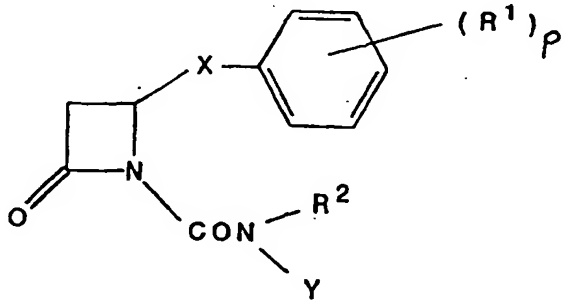
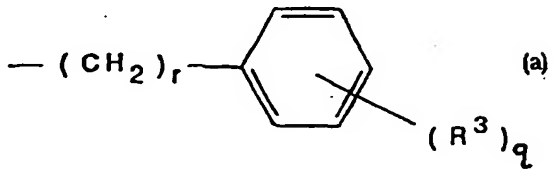
(54) Title: SUBSTITUTED AZETIDINONE AMIDE DERIVATIVES AS ANTI-INFLAMMATORY AND ANTIDEGENERATIVE AGENTS

(57) Abstract

Azetidinone compounds pharmaceutically useful as inhibitors of tumour necrosis factor (TNF) production are disclosed of general formula (I) wherein Y is H, (1-4C)alkyl or (a) and X is thio, sulphinyl or sulphonyl.



(I)



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SUBSTITUTED AZETIDINONE AMIDE DERIVATIVES AS ANTI-INFLAMMATORY AND ANTIDEGENARATIVE AGENTS

This invention concerns amide derivatives and more particularly azetidinone derivatives which are inhibitors of the production of cytokines, in particular of tumour necrosis factor (TNF). The invention also concerns processes for the manufacture of said amide derivatives and pharmaceutical compositions containing them. Also included in the invention is the use of said amide derivatives in the treatment of various diseases including inflammatory and allergic diseases in which the direct or indirect effects of cytokines are involved and the production of new medicaments for such use.

The amide derivatives described hereinafter are inhibitors of the production of TNF which is believed to be formed by the cleavage of a larger precursor or pro-form by the enzyme proTNF Convertase. The amide derivatives of the present invention are inhibitors of TNF production by mechanisms which are believed to include proTNF Convertase inhibition. The term "TNF" is used herein to refer to TNF in general but particularly TNF-alpha.

Excessive TNF production is known to give rise via a cascade of processes to a variety of physiological sequelae including the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans from, for example, cartilage, the stimulation of cell proliferation and to angiogenesis.

It is also known that, in certain cellular systems, TNF production precedes and mediates the production of other cytokines such as interleukin-1 (IL-1) and interleukin-2 (IL-2) which are also believed to contribute to the pathology of disease states such as inflammatory and allergic diseases and cytokine-induced toxicity.

Excessive TNF production has also been implicated in mediating or exacerbating the development of various inflammatory and allergic diseases such as inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease,

ulcerative colitis and gastritis), skin disease (especially psoriasis, eczema and dermatitis) and respiratory disease (especially asthma, bronchitis and allergic rhinitis), and in the production and development of various cardiovascular and cerebrovascular disorders such as myocardial infarction, angina and peripheral vascular disease. Excessive TNF production has also been implicated in mediating complications of bacterial, fungal and/or viral infections such as endotoxic shock, septic shock and toxic shock syndrome. Excessive TNF production has also been implicated in mediating or exacerbating the development of adult respiratory distress syndrome, diseases involving cartilage or muscle resorption, Paget's disease and osteoporosis, pulmonary fibrosis, cirrhosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune deficiency syndrome (AIDS), tumour invasiveness and tumour metastasis.

TNF is also known to cause the activation of latent AIDS.

We have now discovered that certain azetidinone derivatives are effective inhibitors of the production of TNF and this is believed to include inhibition of the enzyme proTNF Convertase; other means of inhibition of TNF production are also contemplated. In International patent application WO 94/00555, published 6-JAN-94, the proTNF convertase enzyme was identified as PR-3, a protease found in leucocyte granules. PR-3 is believed to act on a 26kD transmembrane precursor of mature active 17kD TNF.

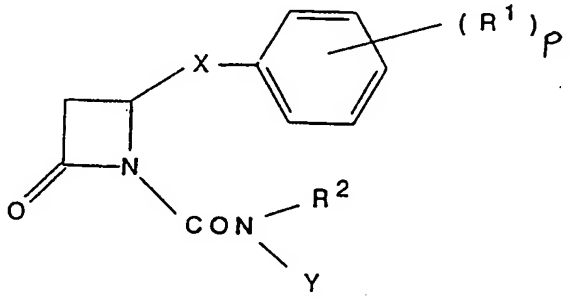
Feldman, Maini et al in Arthritis & Rheumatism, 1993, 36(12), 1681 have described use of a monoclonal antibody to TNF-alpha to treat patients with active rheumatoid arthritis. The treatment was safe and well tolerated with all 20 patients showing significant clinical and laboratory improvements. A further study has been reported (Helmut Fenner. British Connective Tissue Society Meeting on Cytokines and Antagonists, Sheffield . U.K. 28-29 March 1994) on a clinical trial using a soluble TNF receptor fusion protein, TNFp55-IgG, in rheumatoid arthritis which showed similar efficacy to the anti-TNF antibody clinical trial. TNF is thus confirmed as a valid therapeutic target.

Thus such compounds are of value as therapeutic agents in the treatment of diseases or medical conditions mediated alone or in part by TNF. for example, inflammatory and allergic conditions such as

rheumatoid arthritis, osteoarthritis, gout, inflammatory bowel disease, ulcerative colitis and gastritis, skin conditions such as psoriasis, eczema and dermatitis, respiratory conditions such as asthma, bronchitis and allergic rhinitis, cardiovascular and cerebrovascular disorders such as myocardial infarction, angina and peripheral vascular disease, endotoxic shock, septic shock and toxic shock syndrome, adult respiratory distress syndrome, diseases involving cartilage or muscle resorption, Paget's disease, osteoporosis, pulmonary fibrosis, cirrhosis, cachexia, tumour growth and AIDS.

It is known from European Patent Applications Nos. 0 199 630, 0 337 549, 0 481 671 and 0 525 973 that certain azetidin-2-one derivatives possess anti-inflammatory and anti-degenerative properties by virtue of inhibition of the protease enzyme known as elastase. Many of the examples disclosed therein possessed two alkyl substituents at the 3-position of the azetidin-2-one ring and a carbamoyl group at the 1-position. It is believed that none of the 1-carbamoyl substituted azetidin-2-one derivatives disclosed therein was unsubstituted at the 3-position.

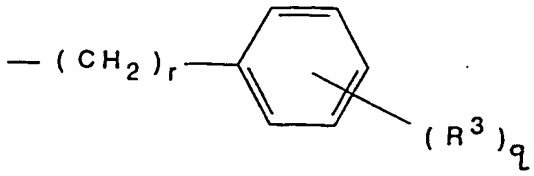
According to the invention there is provided an amide derivative of the formula I



I

wherein X is thio, sulphinyl or sulphonyl;
p is the integer 1 or 2;
each R^1, which may be the same or different, is selected from hydrogen, halogeno, carboxy, carbamoyl, cyano, hydroxy, amino, ureido, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, (2-5C)alkanoyl,

(1-4C)alkoxycarbonyl, halogeno-(1-3C)alkyl, carboxy-(1-3C)alkyl, (1-4C)alkoxycarbonyl-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-(1-4C)alkylcarbamoyl-(1-3C)alkyl, N,N-di-[(1-4C)alkyl]carbamoyl-(1-3C)alkyl and (1-3C)alkylenedioxy;
R^2 is hydrogen; and
Y is hydrogen or (1-4C)alkyl or a group of the formula



wherein r is an integer from 0 to 2 and one of the methylene groups when r is the integer 1 or 2 may optionally bear one or two (1-4C)alkyl substituents;
q is the integer 1 or 2, and
each R^3, which may be the same or different, is selected from hydrogen, halogeno, cyano, hydroxy, amino, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-3C)alkyl and (1-3C)alkylenedioxy;
or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting TNF Convertase or other means of inhibiting TNF production. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Similarly, inhibitory properties against TNF Convertase and/or TNF production may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic terms referred to above include those set out below.

Suitable values for the substituents R^1 or R^3 which may be present on the aryl rings in the compound of the formula I or for substituents on $(CH_2)_r$ include, for example:-

for halogeno:	fluoro, chloro, bromo and iodo;
for (1-4C)alkyl:	methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl;
for (2-4C)alkenyl:	vinyl and allyl;
for (2-4C)alkynyl:	ethynyl and prop-2-ynyl;
for (1-4C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (1-4C)alkylamino:	methylamino, ethylamino, propylamino and butylamino;
for di-[(1-4C)alkyl]amino:	dimethylamino, diethylamino and N-ethyl-N-methylamino;
for (2-4C)alkanoylamino:	acetamido, propionamido and butyramido;
for N-(1-4C)alkyl-(2-4C)-alkanoylamino:	N-methylacetamido, N-ethylacetamido and N-methylpropionamido;
for (2-5C)alkanoyl:	acetyl, propionyl, butyryl and isobutyryl;
for (1-4C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for halogeno-(1-3C)alkyl:	fluorometnyl, chloromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2-chloroethyl and 3-fluoropropyl;
for carboxy-(1-3C)alkyl:	carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;

for (1-4C)alkoxycarbonyl-(1-3C)-alkyl:	methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl;
for carbamoyl-(1-3C)alkyl:	carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;
for N-(1-4C)alkylcarbamoyl-(1-3C)alkyl:	N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 1-(N-ethylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N-ethylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;
for N,N-di-[(1-4C)alkyl]-carbamoyl-(1-3C)alkyl:	N,N-dimethylcarbamoylmethyl, N-ethyl-N-methylcarbamoylmethyl, N,N-diethylcarbamoylmethyl, 1-(N,N-dimethylcarbamoyl)ethyl, 1-(N,N-diethylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 2-(N,N-diethylcarbamoyl)ethyl and 3-(N.N-dimethylcarbamoyl)propyl;
for (1-3C)alkylenedioxy:	methylenedioxy, ethylenedioxy and propylenedioxy.

A suitable value for Y when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl.

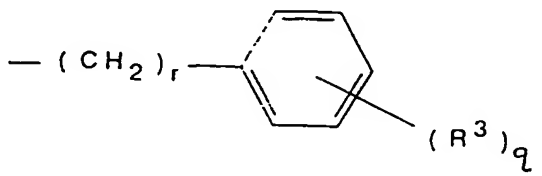
A suitable pharmaceutically-acceptable salt of an amide derivative of the invention is, for example, an acid-addition salt of an amide derivative of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of an amide derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, amide derivatives of the formula I, or pharmaceutically-acceptable salts thereof, wherein the variable groups X, p, R^1, R^2 and Y have the values disclosed hereinbefore or hereinafter in this section defining particular compounds of the invention:-

(a) p is 1 or 2 and each R^1, which may be the same or different, is selected from hydrogen, fluoro, chloro, carboxy, carbamoyl, cyano, hydroxy, amino, ureido, methyl, ethyl, vinyl, allyl, ethynyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, acetamido, N-methylacetamido, acetyl, methoxycarbonyl, ethoxycarbonyl, trifluoromethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and methylenedioxy;

(b) Y is methyl, ethyl, propyl, isopropyl or butyl;

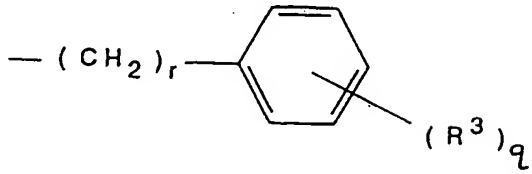
(c) Y is a group of the formula



wherein r is 0 or 1, q is 1 or 2 and each R^3, which may be the same or different, is selected from hydrogen, fluoro, chloro, methyl, ethyl,

methoxy and trifluoromethyl; or

(d) Y is a group of the formula



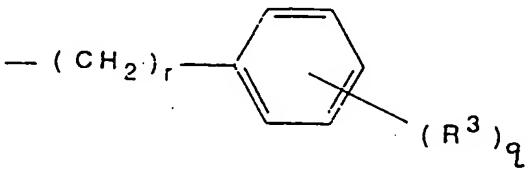
wherein r is 1 and the methylene group may optionally bear one or two substituents selected from methyl, ethyl, propyl and isopropyl, q is 1 or 2 and each R^3, which may be the same or different, is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl.

A preferred compound of the invention is an amide derivative of the formula I wherein X is thio, sulphinyl or sulphonyl; p is 1 or 2 and each R^1, which may be the same or different, is selected from hydrogen, fluoro, chloro, carboxy, carbamoyl, cyano, hydroxy, amino, ureido, methyl, ethyl, methoxy, ethoxy, methylamino, dimethylamino, acetamido, N-methylacetamido, acetyl, methoxycarbonyl, ethoxycarbonyl, trifluoromethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and methylenedioxy;

R^2 is hydrogen; and

Y is methyl, ethyl, propyl, isopropyl or butyl, or

Y is a group of the formula



wherein r is 0 or 1, q is 1 or 2 and each R^3, which may be the same or different, is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl;

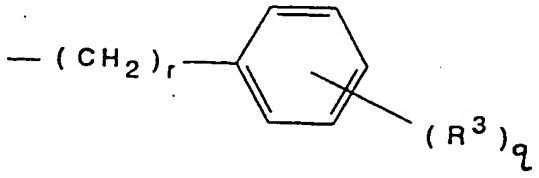
or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention is an amide derivative of the formula I

wherein X is thio;

p is 1 and R^1 is selected from hydrogen, fluoro, chloro, carboxy,

carbamoyl, methyl, methoxy, methoxycarbonyl, ethoxycarbonyl, trifluoromethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl and carbamoylmethyl;
R^2 is hydrogen; and
Y is a group of the formula



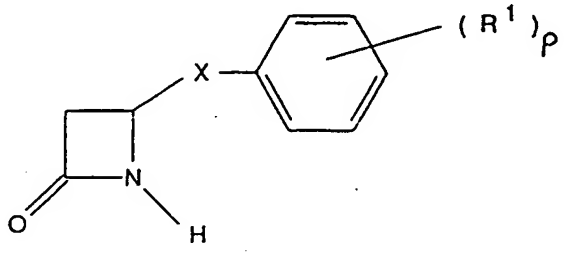
wherein R is 1, q is 1 and R^3 is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

Of the values disclosed herein for substituent R^1, the value when R^1 is carboxy is less preferred.

A specific preferred compound of the invention is the following amide derivative of the formula I
1-(N-benzylcarbamoyl)-4-(phenylthio)azetidin-2-one;
or a pharmaceutically-acceptable salt thereof.

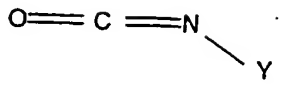
A compound of the invention comprising an amide derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of structurally-related compounds. Such procedures are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, X, p, R^1, R^2 and Y have any of the meanings defined hereinbefore.

(a) The coupling of an azetidin-2-one of the formula II



II

and an isocyanate of the formula III



III

The coupling reaction is conveniently performed in the presence of a suitable base. A suitable base is, for example, an alkali or alkaline earth metal carbonate, (1-4C)alkoxide, (1-4C)alkanoate, hydroxide or hydride, for example sodium carbonate, potassium carbonate, barium carbonate, sodium ethoxide, potassium butoxide, sodium acetate, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride. Alternatively a suitable base for the reaction is, for example, an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene.

The reaction is conveniently performed in a suitable inert solvent or diluent, for example, one or more of pyridine, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxan, methylene chloride, carbon tetrachloride or a dipolar aprotic solvent such as acetone, N,N-dimethylformamide and dimethylsulphoxide. The reaction is conveniently performed at a temperature in the range, for example, 10 to 150°C, conveniently in the range 20 to 60°C.

The starting materials of the formulae II and III may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(b) For the production of those compounds of the formula I wherein X is a sulphinyl or sulphonyl group, the oxidation of a compound of the formula I wherein X is a thio group.

A suitable oxidising agent is, for example, any agent known in the art for the oxidation of thio to sulphinyl and/or sulphonyl, for example, hydrogen peroxide, a peracid (such as 3-chloroperoxybenzoic or peroxyacetic acid), an alkali metal peroxysulphate (such as potassium peroxymonosulphate), a di-(1-4C)alkyldioxiran (such as

dimethyldioxiran), chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is generally carried out under as mild conditions as possible and with the required stoichiometric amount of oxidising agent in order to reduce the risk of over oxidation and damage to other functional groups. In general the reaction is carried out in a suitable solvent or diluent such as methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether and at a temperature, for example, at or near ambient temperature, that is in the range 15 to 35°C. When a compound carrying a sulphinyl group is required a milder oxidising agent may also be used, for example sodium or potassium metaperiodate, conveniently in a polar solvent such as acetic acid or ethanol. It will be appreciated that when a compound of the formula I containing a sulphonyl group is required, it may be obtained by oxidation of the corresponding sulphinyl compound as well as of the corresponding thio compound.

When a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure. When an optically active form of a compound of the formula I is required, it may be obtained by carrying out one of the aforesaid procedures using an optically active starting material, or by resolution of a racemic form of said compound using a conventional procedure.

As stated previously, the compounds of the formula I are believed to include inhibitors of the enzyme proTNF Convertase; the cell based assays described below measure inhibition of TNF production by mechanisms which are believed to include proTNF convertase inhibition. The effects of this inhibition may be demonstrated using one or more of the procedures set out below:-

(a) . An in-vitro assay system involving assessment of the inhibitory effect of a test compound on lipopolysaccharide (LPS)-stimulated production of TNF in immature cells of the human myelomonocytic cell line THP-1 [American Type Culture Collection (ATCC) TIB 202 deposited by S. Tsuchiya, Tohoku University, Sendai, Japan; Int. J. Cancer, 1980, 26, 171, Cellular Immunol., 1991, 138, 1].

THP-1 cells [$4x10^5$ cells in 160 µl of RPMI 1640 medium (Gibco

Catalogue No. 041-01870) supplemented with penicillin (100 units per ml), streptomycin (100 µg/ml) and glutamine (2 mM)] and test compound (20 µl of various concentrations of test compound in a mixture of DMSO and RPMI medium) were incubated at 37°C for 30 minutes prior to the addition of E. Coli 0111:B4 LPS (obtained from Sigma, Catalogue No. L-4130; 20 µl giving a final concentration of 50 µg/ml). The cells were incubated for 6 hours. Portions (20 µl) of the supernatant solution were assayed for TNF using a modification of a sandwich-ELISA procedure as described in Methods in Enzymology, 1980, Vol. 70, 419. The assay involved a sheep IgG anti-human TNFα antibody as the capture antibody, a rabbit IgG anti-human TNFα antibody and an affinity chromatography purified sheep anti-rabbit IgG antibody conjugated to horseradish peroxidase (obtained from ICN Inc., Catalogue No. ICN 68-397) as the detecting antibody. Urea peroxide substrate was added and TNFα levels were calculated based on a standard curve generated using recombinant human TNFα. The assay detects levels of TNFα of 50 pg/ml and above.

(b) An in-vitro assay system involving assessment of the inhibitory effect of a test compound on LPS-stimulated production of TNF in whole human blood using routine modifications of the method described in Lymphokine Research, 1989, 8, 141.

Human blood diluted five fold in RPMI 1640 medium containing penicillin (100 units per ml), streptomycin (100 µg/ml) and glutamine (2 mM) to give a volume of 160 µl and test compound (20 µl of various concentrations of test compound in a mixture of DMSO and RPMI medium) were incubated at 37°C for 30 minutes prior to the addition of E. Coli 0111:B4 LPS (20 µl giving a final concentration of 10 µg/ml). The mixture was incubated for 6 hours, centrifuged and portions of the supernatant plasma were assayed for TNFα by way of the sandwich-ELISA assay procedure described hereinbefore.

Although the pharmacological properties of the compounds of the formula I vary with structural change as expected, in general compounds of the formula I possess activity at the following concentrations or doses in at least one of the above tests (a) and (b):-

Test (a): IC_{50} (TNFα) in the range, for example, 1 to 200 μM;
Test (b): IC_{50} (TNFα) in the range, for example, 1 to 500 μM.

Thus by way of example, the compound 1-(N-benzylcarbamoyl)-4-(phenylthio)azetidin-2-one has an IC_{50} of approximately 22 μM in Test (a) and an IC_{50} of approximately 35 μM in Test (b). No toxicity was observed for compounds tested of the present invention.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises an amide derivative of the formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is an amide derivative of the formula I, or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

According to a further feature of the invention there is provided an amide derivative of the formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The invention also includes a method of treating a disease or medical condition mediated alone or in part by tumour necrosis factor (TNF) which comprises administering to a warm-blooded animal requiring such treatment an effective amount of an active ingredient as defined above. The invention also provides the use of such an active ingredient in the production of a new medicament for use in a TNF mediated disease or medical condition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of TNF.

In using a compound of the formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used.

Although the compounds of the formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of TNF. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The compositions of the invention may in addition contain one or more therapeutic or prophylactic agents known to be of value for the disease under treatment. Thus, for example, in the treatment of

inflammatory conditions, a known cyclooxygenase inhibitor (such as indomethacin, acetylsalicyclic acid, diclofenac, flurbiprofen and piroxicam), a known inhibitor of the enzyme 5-lipoxygenase (such as zileuton and the compounds disclosed in European Patent Application No. 0385662) or a known disease-modifying agent (such as methotrexate and penicillamine) may usefully also be administered, whether simultaneously, sequentially or separately, with the compositions of the invention. In the treatment of allergic and respiratory conditions, a known anti-histamine (such as astemizole and terfenadine), steroid (such as beclomethasone dipropionate and betamethasone), beta-adrenergic stimulant (such as salbutamol and salmeterol), anti-inflammatory (such as sodium cromoglycate and nedocromil sodium) or a known leukotriene antagonist (such as the compounds disclosed in European Patent Application No. 0199543) may usefully also be administered, whether simultaneously, sequentially or separately, with the composition of the invention. In the treatment of cardiovascular and cerebrovascular disorders, a known anti-hypertensive agent (for example a beta-adrenergic blocker, diuretic, vasodilator, inhibitor of angiotensin-converting enzyme, calcium antagonist or an angiotensin antagonist), platelet aggregation inhibitor (such as aspirin) or hypolipidaemic agent (such as cholestyramine and simvastatin) may usefully also be administered, whether simultaneously, sequentially or separately, with the composition of the invention. In the treatment of endotoxic, septic or toxic shock syndrome, a known antibacterial, antifungal or antiviral agent, an inhibitor of nitric oxide release or an adrenergic stimulant (such as adrenaline) may usefully also be administered, whether simultaneously, sequentially or separately, with the composition of the invention. In the treatment of Paget's disease or osteoporosis, a known oestrogen (such as ethinyloestradiol), a diphosphonic acid (such as disodium etidronate) or calcitonin may usefully also be administered, whether simultaneously, sequentially or separately, with the composition of the invention. In the treatment of cachexia, a known antagonist of 5-hydroxytryptamine (such as ondansetron) and in the treatment of cancer, a known cytotoxic agent (such as methotrexate, 5-fluorouracil and taxol) or a hormone antagonist (such as tamoxifen) may usefully

also be administered, whether simultaneously, sequentially or separately, with the composition of the invention.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the end-products of the formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques; unless otherwise stated, $CDCl_3$ solutions of the end-products of the formula I were used for the determination of NMR spectral data, chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; m, multiplet;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviation has been used:-

DMF N,N-dimethylformamide.

Example 1

Benzyl isocyanate (0.07 ml) was added to a stirred mixture of 4-(phenylthio)azetidin-2-one (0.1 g), triethylamine (0.7 ml) and DMF (1.5 ml). The mixture was stirred at ambient temperature for 15 minutes. The mixture was partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using ethyl acetate as eluent. There was thus obtained 1-(N-benzylcarbamoyl)-4-(phenylthio)azetidin-2-one (0.094 g, 54%), m.p. 81-83°C;

NMR Spectrum (CD_3SOCD_3) 2.8 (m, 1H), 3.5 (m, 1H), 4.3 (m, 2H), 5.4 (m, 1H), 7.2-7.5 (m, 10H);

Elemental Analysis: Found C, 65.4; H, 5.2; N, 8.9;

$C_{17}H_{16}N_2O_2S$ requires C, 65.4; H, 5.2; N, 9.0%.

The 4-(phenylthio)azetidin-2-one used as a starting material was obtained as follows:-

A 2N aqueous sodium hydroxide solution (2.1 ml) was added dropwise to a stirred mixture of 4-acetoxyazetidin-2-one (0.5 g), thiophenol (0.6 g), water (0.1 ml) and ethanol (2.8 ml) which had been cooled to -5°C. The mixture was stirred at 0°C for 1 hour. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using ethyl acetate as eluent. There was thus obtained 4-(phenylthio)azetidin-2-one (0.3 g, 43%), m.p. 65-66°C;

NMR Spectrum (CD_3SOCD_3) 2.75 (m, 1H), 3.35 (m, 1H), 5.1 (m, 1H), 7.4-7.5 (m, 5H), 8.7 (broad s, 1H).

Example 2

4-(Phenylthio)azetidin-2-one (0.3 g) was dissolved in 5 ml DMF. Triethylamine (0.23 ml) and isopropylisocyanate (0.14.g) were added under Argon and the mixture stirred at room temperature for 1 hour at which point tlc indicated a product had formed. The mixture was washed in water, product extracted into ethylacetate, dried, chromatographed using hexane: ethylacetate (1:1) to give the desired product 1-(N-isopropylcarbamoyl)-4-(phenylthio)azetidin-2-one as a clear gum (0.25 g, 57%); molecular weight by mass spectrometry 264; elemental analysis: required, 59.1 C, 6.1 H, 10.6 N; found 58.6 C, 6.3 H, 10.5 N.

The 4-(phenylthio)azetidin-2-one used as starting material was obtained as described in Example 1.

Example 3

4-(3-Bromophenylthio)azetidin-2-one (0.2 g) was dissolved in DMF (3 ml), triethylamine (1 ml) added, then benzylisocyanate (0.103 g) under Argon and the mixture stirred at room temperature for 1½ hours. The mixture was washed in water, product extracted into ethylacetate, dried, chromatographed using hexane: ethyl acetate (1:1) to obtain the desired product 1-(N-benzylcarbamoyl)-4-(3-bromophenylthio)azetidin-2-one as a white gum which did not crystallise on scratching (0.206 g, 67.5%).

Molecular weight by mass spectroscopy 390

Elemental analysis: required C 52.2, H 3.86, N 7.16; found C 52.6, H 4.00, N 7.00.

NMR: δ 2.5 DMSO; δ 3 H_2O

δ 2.9/3.0 (dd) -CH_2- C(O) 1H

δ 3.55/3.65 (dd) -CH_2- C(O) 1H

δ 4.3 (octet) NH-CH_2-Ph 2H

δ 5.5>CH-S-Ph 1H q

δ 7.2 Ar 6 H

δ 7.5 Ar 3 H

δ 7.8 NH-CH_2-Ph (t) 1H

The 4-(3-bromophenylthio)azetidin-2-one used as starting material was obtained as follows. 4-(acetoxy)azetidin-2-one (0.5 g) was dissolved in ethanol (10 ml) and cooled using an ice bath, 1-thio-3-bromobenzene (1.02 g) added under argon followed by NaOH (4.26 ml of 2M solution) ensuring the temperature remained about 0°C and the mixture stirred in an ice bath overnight. Ethanol was removed under vacuum, residue washed with water, extracted into ethyl acetate, dried, solvent removed and the colourless liquid remaining chromatographed using hexane: ethylacetate (1:1) to give the desired starting material as a white solid after scratching (0.55 g, 55%), melting point 55-56°C, molecular weight by mass spectrum 256.

NMR: δ 2.5, DMSO; δ 3.3 H_2O

δ 2.8/2.9-CH_2- C(O) 1H (dd)

δ 3.4/3.5-CH_2- C(O) 1H (dd)

δ 5.2 >C(H)-S- C(O) 1H (q)

δ 7.3/7.7 - Ar 4H

δ 8.8 - NH-ring 1H (s)

Example 4

4-(4-Tert-butyl-phenylthio)azetidin-2-one (0.25 g) was dissolved in DMF (3 ml), triethylamine (1.36 ml) added, followed by benzylisocyanate (0.141 g) under argon and the mixture stirred at room temperature for 30 minutes. The mixture was washed in water, product extracted into ethylacetate, solvent dried and removed to leave the product as a yellow oil which was chromatographed using hexane: ethylacetate (1:1). The purified product 1-(N-benzylcarbamoyl)-4-(3-tertbutylphenylthio)azetidin-2-one gave a white solid on scratching (0.258 g, 66%). Melting point 102-104°, molecular weight by mass spectrometry 368, elemental analysis: required C 68.4, H 6.56, N 7.60; found C 67.9, H 6.5, N 7.4.

NMR:

δ 1.3 Ph-C(CH_3)$_3$ 9H, s.

δ 2.5 DMSO δ 3.3 H_2O

δ 2.7/2.8 (dd)-CH_2- C(O) 1H

δ 3.5/3.6 (dd) -CH_2- C(O) 1H

δ 4.4 (octet) NH-CH_2-Ph 2H

δ 5.4 (q) -C(H)-S- 1H
δ 7.2/7.5 Ar 9H
δ 7.5 (t) C(O)-NH-CH_2 1H

The 4-(4-Tert-butyl-phenylthio)azetidin-2-one used as starting material was obtained as follows.

4-acetoxyazetidin-2-one (0.5 g) was dissolved in ethanol (10 ml), cooled to 0° in an ice bath, 1-thio-4-tertbutylbenzene (0.9 g) added, followed by NaOH (2.13 ml of 2M solution) whilst ensuring the temperature stayed below 5° and the mixture stirred at room temperature for 1 hour. Ethanol was removed under vacuum, residue washed in water, extracted into ethyl acetate; dried, and solvent removed to leave a gum which was chromatographed with hexane: ethylacetate (1:1) to give the desired starting material as a white solid (0.52 g, 57%). Melting point 89-91°C, molecular weight by mass spectrometry, 235.
NMR: δ 1.25 (s) 9H.
δ 2.5 DMSO, δ 3.3 H_2O,
δ 2.7/2.8 (dd) -CH_2- C(O) 1H
δ 3.3/3.4 (dd) -CH_2- C(O) 1H
δ 5.0 (q) >CH-S- 1H
δ 7.4/7.3 Ar 4H
δ 8.7 (s) -NH- 1H

Example 5

4-(3-Bromophenylsulphonyl)azetidin-2-one (0.1 g) was dissolved in DMF (2 ml), triethylamine (0.5 ml) added followed by benzylisocyanate (0.046 g) under argon and the mixture stirred at room temperature for 2½ hours. The mixture was washed in water and product extracted into ethyl acetate, dried and solvent removed to leave a yellow liquid which was chromatographed using hexane: ethylacetate (1:1). The desired product 1-(N-benzylcarbamoyl)-4-(3-bromophenyl-sulphonyl)azetidin-2-one was obtained as a white solid (0.074 g, 50.7%). Melting point 119-123°.
Molecular weight by mass spectrometry 422

NMR:

δ 2.5 DMSO; δ 3.3 H_2O

δ 3.4/3.5 (dd) $-CH_2-$ C(O) 1H

δ 3.6/3.7 (dd) $-CH_2-$ C(O) 1H

δ 4.2 (d) -NH-CH_2-Ph 2H

δ 5.6 (q) >C(H)-S 1H

δ 7.2/7.3 Ar

δ 7.6 Ar (t)

δ 7.7 (t) C(O)-NH-CH_2 1H

δ 7.9-8.1 Ar

The 4-(3-bromophenylsulphonyl)azetidin-2-one used as starting material was obtained as follows:

4-(3-bromophenylthio)azetidin-2-one (0.2 g; obtained as described in Example 3) was dissolved in methanol (10 ml), potassium peroxymonosulphate (0.94 g in 5 ml H_2O and sodium acetate to pH5-6) added while mixing at room temperature; a white precipitate formed immediately. After 2½ hours solvent was removed under vacuum to leave a white solid which was washed in water and extracted into ethyl acetate, dried and solvent removed to leave the desired starting material as a white solid (160 mg, 71%). Melting point 139-143°; molecular weight by mass spectrometry 288.

NMR:

δ 2.5 DMSO δ 3.3 H_2O

δ 3.0/3.1 (dd)-CH_2- C(O) 1H

δ 3.3/3.4 (dd)-CH_2- C(O) 1H

δ 5.2 (q) >C(H)-S- 1H

δ 7.6 (t) Ar 1H

δ 7.9/8.1 (m) Ar 3H

δ 9.0 (S) -NH- 1H

Example 6

4-(4-Fluorophenylthio)azetidin-2-one (0.25 g) was dissolved in DMF (3 ml), triethylamine (1.6 ml) added, then benzylisocyanate (0.17 g) and the mixture stirred under argon at room temperature for 2 hours. The mixture was washed in water, extracted into ethylacetate,

dried and solvent removed to leave a yellow liquid which was chromatographed using hexane: ethyl acetate (1:1) to give the desired product 2-(4-fluorophenylthio)-4-oxo-azetidine-1-carboxylic acid benzyl amide as a white solid on scratching (0.272 g, 65%). Melting point 86-88°; molecular weight by mass spectrometry 330; elemental analysis: required C 61.8, H 4.58, N 8.48; found C 61.8, H 4.7, N 8.40.
NMR:
δ 2.5 DMSO δ 3.3 H_2O
δ 2.7/2.8 (dd) -CH_2- C(O) 1H
δ 3.5/3.6 (dd) -CH_2- C(O) 1H
δ 4.3 (octet) NH-CH_2-Ph 2H
δ 5.38 (q) >C(H)-S- 1H
δ 7.1-7.5 Ar 9H; C(O)-NH-CH_2- 1H

The 4-(4-fluorophenylthio)azetidin-2-one used as starting material was obtained as follows. Acetic acid 4-oxo--azetidin-2-yl ester (0.5 g) was dissolved, in ethanol (10 ml) and cooled to 0° in an ice bath, 4-fluorobenzenethiol (0.7 g) added, then NaOH (2.13 ml of 2M solution) whilst keeping the temperature below 5° and the mixture stirred for 2½ hours. Ethanol was removed under vacuum, product extracted into ethyl acetate, dried and solvent removed to leave a clear gum which was chromatographed using hexane: ethyl acetate (1:1) to give the desired starting material as a white solid (0.4 g, 52%). Melting point 69-71°; molecular weight by mass spectrometry 197.

Example 7

4-o-Tolylsulfanyl-azetidin-2-one (0.2 g) was dissolved in DMF, triethylamine (1.3 ml) added, then benzylisocyanate (0.138 g) and the mixture stirred under argon overnight. The mixture was washed in water, product extracted into ethyl acetate, dried and solvent removed to leave a yellow liquid which was chromatographed in hexane:ethyl acetate (1:1) to give the desired product 2-oxo-4-o-tolylsulfanyl-azetidine-1-carboxylic acid benzylamide as a gum (0.21 g, 61.8%) which on scratching gave a solid. Melting point 48-49°.

NMR:
δ 2.3
δ 2.5 DMSO
δ 2.7/2.8 (dd) $-CH_2-$ C(O) 1H
δ 3.3 H_2O
δ 3.5/3.6 (dd) $-CH_2-$ C(O) 1H
δ 4.3 (octet) -NH-$C\underline{H}_2$-Ph 2H
δ 5.4 >$C\underline{H}$-S- 1H
δ 7.1-7.5 Ar
δ 7.5/7.6 (t) -C(O)-$N\underline{H}$-CH_2-Ph 1H

The 4-o-Tolylsulfanyl-azetidin-2-one used as starting material was obtained as follows. Acetic acid 4-oxo-azetidin-2-yl ester (0.25 g) was dissolved in ethanol (3 ml), cooled to 0°, 2-thiocresol (0.336 g) added, then NaOH (1.06 ml of 2M solution) and the mixture stirred at 0°C for 2h. Ethanol was removed under vacuum, washed in water, product extracted into ethyl acetate, dried and solvent removed to leave a clear liquid which was chromatographed using hexane: ethylacetate (1:1) to give the desired starting material as a solid (0.277 g, 74%). Melting point 66-69°; molecular weight by mass spec. 193.

NMR:
2.5 DMSO
δ 2.3 Ar-$C\underline{H}_3$ 3H (s)
δ 2.7/2.8 $-CH_2-$ C(O) (dd) 1H
3.3 H_2O
δ 3.4/3.5 $-CH_2-$ C(O) (dd) 1H
δ 5.1 >CH-S- (q) 1H
δ 7.2/7.4 Ar 4H (m)
δ 8.7 >$N\underline{H}$ ring 1H

Example 8

4-(4-Methoxyphenylsulfanyl)-azetidin-2-one (0.25 g) was dissolved in DMF (3 ml), triethylamine (1.5 ml) added, then benzyl isocyanate (0.158 g) and the mixture stirred under argon overnight. The mixture was washed in water, extracted into ethyl acetate, dried

and solvent removed to give an orange liquid which was chromatographed in hexane:ethylacetate (1:1) to give the product 2-(4-methoxyphenyl-sulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide as a white solid (0.296 g, 72%). Melting point 100-102°C; molecular weight by mass spec. 342; elemental analysis: required C 63.1, H 5.3, N 8.18; found C 63.3, H 5.4, N 8.0.

NMR:

δ 2.5 DMSO δ 3.3 H_2O

δ 2.6/2.7 (dd) -CH_2- C(O) 1H

δ 3.4/3.5 (dd) -CH_2- C(O) 1H

δ 3.76 Ar-O-CH_3 3H

δ 5.25 >C(H)-S (q) 1H

δ 4.36 (d) NH-CH_2-Ph 2H

δ 6.9 (d) Ar (p) 2H

δ 7.3/7.4 Ar 7H

δ 7.5 (t)-C(O)-NH-CH_2 1H

The 4-(4-Methoxyphenylsulfanyl)-azetidin-2-one used as starting material was obtained as follows. Acetic acid 4-oxo-azetidin-2-yl ester (0.3 g) was dissolved in ethanol (7 ml), cooled to 0°, 1-thio-4-methoxy-benzene (0.46 g) added, then base under argon and the mixture was stirred at 0°C for 2h. Solvent was removed, residue extracted into ethyl acetate, washed with water, dried and solvent removed to leave a pale yellow gum which was chromatographed using hexane: ethyl acetate (1:1) to give the desired starting material as a white solid (0.347 g, 71%). Melting point 73-76°, molecular weight by mass spec = 210.

NMR:

δ 2.5 DMSO, δ 3.3 H_2O

δ 2.6/2.7 (dd) CH_2-C(O) 1H

δ 3.2/3.3 (dd) CH_2-C(O) 1H

δ 3.7/3.8 (s) -Ar-O-Me 3H

δ 4.9 (q) >CH-S 1H

δ 6.9/7.0 (d) Ar(p) 2H

δ 7.4 d Ar(p) 2H

δ 8.57 (s) >NH 1H

Example 9

N[4-(4-oxo-azetidin-2-ylsulfanyl)-phenyl]acetamide (0.21 g) was dissolved in DMF (1.5 ml), triethylamine (0.68 ml) added, then benzylisocyanate (0.14 g) under argon and the mixture stirred overnight at room temperature. The mixture was washed with water, extracted into ethyl acetate, dried and solvent removed to leave a yellow liquid which was chromatographed using ethyl acetate: hexane (1:1) to give the desired product 2-(4-acetylamine-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzyl amide as a yellow liquid which partially crystallised. NMR and mass spectrometry indicated some impurity present. The product was re-chromatographed in ethyl acetate to give 0.104 g of product, melting point 43-46°, molecular weight by mass spec. 369.

The N[4-(4-oxo-azetidin-2-ylsulfanyl)-phenyl]acetamide used as starting material was obtained as follows. Acetic acid 4-oxo-azetidin-2-yl ester (0.3 g) was dissolved in ethanol (7 ml), cooled to 0°C, N-(4-mercaptophenyl)acetamide added (0.54 g), then NaOH (1.3 ml of 2M solution) and the mixture stirred at 0° for 2 hours. Ethanol was removed under vacuum, residue washed with 2M NaOH (0.7 ml in 10 ml water), extracted with ethylacetate and solvent removed to give the desired starting material as a yellow solid (0.251 g, 46%).

Example 10

4-p-Tolylsulfanyl-azetidin-2-one (0.2 g) was dissolved in DMF (1.5 ml), triethylamine (0.68 ml) added, then benzylisocyanate (0.14 g) under argon and the mixture stirred for 2 hours at room temperature. The mixture was washed with water, extracted into ethylacetate, dried and solvent removed to give a yellow liquid which on chromatography in ethyl acetate: hexane (1:1) gave the desired product 2-oxo-4-p-tolylsulfanyl-azetidine-1-carboxylic acid benzylamide as a clear gum which crystallised on scratching to give a white solid (0.115 g, 33%). Melting point 68-69°, molecular weight by mass spec. 326, Elemental Analysis: required C 66.2, H 5.56, N 8.58, found C 66.5, H 5.60, N 8.30.

NMR:
δ 2.3 (s) Ar-CH_3 3H
δ 2.5 DMSO
δ 2.7/2.8 (dd) -CH_2- C(O) 1H
δ 3.3 (S) H_2O
δ 3.4/3.5 (dd) -CH_2- C(O) 1H
δ 4.4 (d) NH-CH_2-Ph 2H
δ 5.3 (q) >CH-S- 1H
δ 7.1/7.3 Ar
δ 7.5 (t) -NH-CH_2-Ph 1H

The 4-p-tolylsulfanyl-azetidin-2-one used as starting material was obtained as follows. Acetic acid 4-oxoazetidin-2-yl ester (0.25 g) was dissolved in ethanol (4 ml), 4-thio-cresol (0.26 g) added under argon, then NaOH (1.06 ml of 2M solution) and the mixture stirred at room temperature for 1 hour. Ethanol was removed under vacuum, residue washed in water, extracted into ethyl acetate, dried and solvent removed to give the desired starting material as a white solid (0.374 g, 54.5%). Melting point 98-100°.
NMR: δ 2.25/2.3 Ar-CH_3 3H
δ 2.5 DMSO
δ 2.6/2.7 (dd) -CH_2- C(O) 1H
δ 3.3 H_2O
δ 3.4 -CH_2- C(O) 1H
δ 5.0 >CH-S-Ar 1H
δ 7.2 d Ar (p) 2H
δ 7.4 d Ar (p) 2H
δ 8.7 (s) >N-H 1H

Example 11

4-(3-Chlorophenylsulfanyl)-azetidin-2-one (0.25 g) was dissolved in DMF (2.5 N), triethylamine added (0.75 ml) under argon, then benzylisocyanate (0.14 ml) and the mixture stirred at room temperature for 30 minutes. The mixture was washed with water, extracted into ethylacetate, dried and solvent removed to give a gum which was chromatographed using hexane:ethylacetate (1:1) to yield the

product 2-(3-chloro-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide as a clear gum which produced a white solid on scratching (0.155 g, 38%). Melting point 57-58°, molecular weight by mass spec. 346, Elemental Analysis: required 58.9 C, 4.36 H, 8.08 N; found 59.0 C, 4.30 H, 7.90 N.

NMR: δ 2.5 DMSO δ 3.3 H_2O

δ 2.9/3.0 dd $-CH_2-$ C(O) 1H

δ 3.5/3.6 dd $-CH_2-$ C(O) 1H

δ 5.5 q >CH-S- 1H

δ 4.3 octet; NH-CH_2-Ph 2H

δ 7.2/7.6 Ar, C(O)-NH-CH_2 10H

The 4-(3-chlorophenylsulfanyl)-azetidin-2-one used as starting material was obtained as follows. Acetic acid 4-oxoazetidin-2-yl ester (0.25 g) was dissolved in ethanol (4 ml), 3-chlorobenzenethiol added (0.31 g) under argon, then NaOH (1.06 ml of 2M solution) and the mixture stirred at room temperature for 3 hours. Ethanol was removed, residue washed in water and extracted into ethyl acetate, dried and solvent removed to give the desired starting material (approx. 0.25 g, 60%).

Example 12

The product 2-(3-methoxy-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide was prepared by reacting 4-(3-methoxy-phenylsulfanyl)-azetidin-2-one (0.25 g) and benzylisocyanate (0.158 g) by methods analogous to that set out in Example 8. Yield 0.184 g, (45%). Elemental Analysis: required C 63.1, H 5.30, N 8.18; found C 63.4, H 5.40, N 7.80.

NMR: δ 1.25/2.01/4.05 EtOAc

δ 2.5 DMSO, δ 3.3 H_2O

δ 2.8/2.9 (dd) $-CH_2-$ C(O) 1H

δ 3.5/3.6 (dd) $-CH_2-$ C(O) 1H

δ 4.3 (octet) NH-CH_2-Ph 2H

δ 5.5 (q) >CH-S- 1H

δ 6.9/7.3 Ar 9H

δ 7.6 (t) C(O)-NH-CH_2 1H

The 4-(3-methoxy-phenylsulfanyl)-azetidin-2-one (0.25 g) used as starting material was obtained in analogous manner to the corresponding step in Example 8. The following reagents were used: acetic acid 4-oxo-azetidin-2-yl ester (0.25 g); 3-methoxybenzenethiol (0.298 g); NaOH (1.06 ml) and ethanol (4 ml). The desired starting material was obtained as a colourless gum (0.28 g).

Examples 13 & 14

4-Phenylsulfanyl-azetidin-2-one (179 mg) was dissolved in DMF (2.7 ml) under argon, triethylamine (0.125 ml) added, then R-(1-isocyanato-ethyl) benzene (140 µl; Fluka) and stirred for 60 minutes at room temperature. Water was added to the mixture, residue extracted with ethyl acetate, washed in water (x3) and saturated salt (x1), dried and evaporated. The product was subjected to flash chromatography using ethyl acetate: hexane (1:3) to give the desired products as two bands (top and bottom) with a combined yield of 83%. The desired products were 2-oxo-4(R)phenylsulfanyl-azetidine-1-[N-(R)-1-phenylethyl]-carboxamide and 2-oxo-4(S)phenylsulfanyl-azetidine-1-[N-(R)-1-phenylethyl]-carboxamide. The top band crystallised in ether to give white crystals (70 mg) with a melting point of 80-82°.
Elemental Analysis: required C 66.2, H 5.56, N 8.55; found (top band) C 66.4, H 5.7, N 8.6; found (bottom band) C 66.2, H 5.7, N 8.4.

The starting material 4-Phenylsulfanyl-azetidin-2-one was obtained as described in Example 1.

Example 15 & 16

Examples 13 & 14 were repeated in an analogous manner but substituting the S isomer of (1-isocyanato-ethyl)benzene (Fluka). A combined yield for the two isomers of 74% was obtained (117 mg of top band, 125 mg of bottom band). The desired two isomers were 2-oxo-4(R)-phenylsulfanyl-azetidine-1-[N-(S)-1-phenylethyl]-carboxamide and 2-oxo-4(S)phenylsulfanyl-azetidine-1-[N-(S)-1-phenylethyl]-carboxamide.
Elemental Analysis: required C 66.2, H 5.56, N 8.58, found (top band) C 66.3, H 5.8, N 8.5; found (bottom band) C 66.1, H 5.9, N 8.1.

Example 17

An analogous procedure to that set out in Examples 13 & 14 was performed. The following reagents were used: 4-phenylsulfanyl-azetidin-2-one (179 mg); 1-chloro-4-isocyanato-benzene (very hygroscopic; 169 mg); triethylamine (0.125 ml) and; DMF (2.7 ml). The desired product 2-oxo-4-phenylsulphanyl-azetidine-1-(N-4-chlorophenyl)carboxamide was obtained as a white solid (160 mg; 48%). Elemental Analysis: required C 57.7, H 3.94, N 8.3; found C 57.6, H 3.9, N, 8.3.

Example 18

An analogous procedure to that set out in Examples 13 & 14 was performed. The following reagents were used: 4-phenylsulfanyl-azetidin-2-one (179 mg); 1-isocyanato-4-methoxybenzene (142 µl); triethylamine (0.125 ml) and; DMF (2.7 ml). The desired product 2-oxo-4-phenylsulfanyl-azetidine-1-(N-4-methoxyphenyl)-carboxamide was obtained as a white solid (230 mg, 70%). Elemental Analysis: required C 62.2, H 4.91, N 8.53; found C 62.0, H 4.9, N 8.4.

Example 19

An analogous procedure to that set out in Example 8 was performed. The following reagents were used: 4-(3-methyl-phenylsulfanyl)-azetidin-2-one (0.3 g); benzylisocyanate (0.19 ml); triethylamine (0.2 ml) and DMF (4 ml). A yellow gum was produced which was purified by chromatography to give the desired product 2-(3-methyl-phenylsulfanyl)-4-oxo-azetidine-1-carboxylic acid benzylamide as a white solid (0.285 g, 56%). Melting point 56-58°C; Elemental Analysis: required C 66.2, H 5.56, N 8.58; found C 66.3, H 5.60, N 8.70;
Molecular weight by mass spec. 326.
NMR: δ 2.27 (s)-Ar-CH_3 3H
δ 2.7/2.8 (d)-CH_2- C(O) 1H
δ 3.5/3.6 (d)-CH_2- C(O) 1H
δ 4.4 (d) NH-CH_2-Ph 2H
δ 5.4 (q) >CH-S- 1H

δ 7.2/7.4 (m) Ar 9H
δ 7.5 (t) -NH-CH_2- 1H

The starting material 4-(3-methyl-phenylsulfanyl)-azetidin-2-one (0.3 g) was obtained in an analogous manner to the corresponding step in Example 8. The following reagents were used: acetic acid 4-oxo-azetidin-2-yl ester (0.5 g); 3-thiocresol (0.64 ml); NaOH (2.12 ml) and ethanol (8 ml). The reagents were mixed for 1 hour, then further portions of NaOH and acetic acid 4-oxo-azetidin-2-yl ester (0.5 g) were added and mixed for a further 30 minutes. The desired starting material was obtained as a gum (0.376 g, 50%). Molecular weight by mass spec. 193.
NMR: δ 2.3 Ar-CH_3 3H
δ 2.7/2.8 -CH_2- C(O) 1H
δ 3.4 -CH_2- C(O) 1H
δ 5.1 >CH-S 1H
δ 7.2/7.4 Ar 4H
δ 8.7 NH 1H

Example 20

Triethylamine (0.17 ml) and diphenylphosphonylazide (0.34 g) were added under argon to 3-cyanophenylacetic acid (0.2 g) in dichloromethane (0.3 ml); the mixture was stirred at room temperature for 3 hours, then heated to reflux for 2 hours. 4-(3-bromophenylsulfanyl)-azetidin-2-one (0.103 g; see Example 3) and triethylamine (0.085 ml) were added and the mixture cooled to room temperature and stirred overnight. The mixture was washed in water etc. to purify the desired product as described in the corresponding steps of Example 8. The product 2-(3-bromo-phenylsulfanyl)-4-oxo-1-(N-3-cyanobenzyl)carboxamide was obtained as a red gum (0.184 g). Molecular weight by mass spec. 416.

Example 21

4-(Phenylsulfanyl)azetidin-2-one (0.3 g), phenylisocyanate (0.199 g), triethylamine (0.17 g) and DMF (5 ml) were reacted and product purified, in an analogous manner to the corresponding steps in

Example 8. The desired product 4-(phenylsulfanyl)azetidin-2-one-1-(N-phenyl)carboxamide was obtained as a pale yellow gum (0.217 g, 43%). Molecular weight by mass spec. 298; Elemental Analysis: required C 64.4, H 4.73, N 9.39; found C 64.4, H 4.90, N 9.20.

NMR: δ 2.8/2.9 (dd) $-CH_2-$ C(O) 1H

δ 3.6/3.5 (dd) $>CH_2-$ C(O) 1H

δ 5.6 (m) >CH-S- 1H

δ 7.1 Ar ~10H

δ 7.2/7.5 Ar ~1H

δ 8.9 (s) NH Ph

The 4-(phenylsulfanyl)azetidin-2-one used as starting material was obtained as described in Example 1.

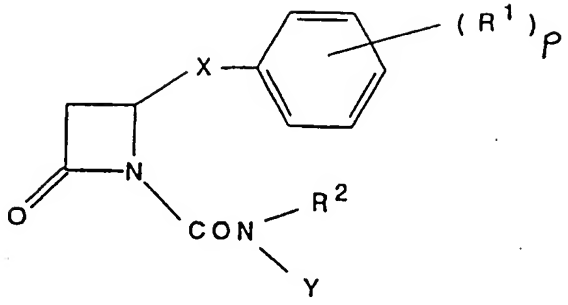
Example 22

1-(N-benzylcarbamoyl)-4-(phenylthio)azetidin-2-one (97 mg; prepared as described in Example 1) in methanol (2.5 ml) was stirred at room temperature and potassium peroxymonosulphate (300 mg in 1.5 ml water; Tet. Lett. 22 (14), 1981: 1287) added and left overnight. A further 200 mg of potassium peroxymonosulphate was added and the mixture heated in an oil bath at 70° for 5 hours, cooled and diluted in aqueous K_2CO_3/ethyl acetate. The organic layer was separated and the aqueous residue washed twice in ethyl acetate. The combined organic fractions were washed with saturated NaCl, dried and product dissolved in warm ethyl acetate and purified by chromatography in ethyl acetate: hexane (2:3). The desired product 1-(N-benzylcarbamoyl)-4-(phenylsulphonyl)azetidin-2-one was obtained (70 mg, 66%). Melting point 137-9°; Elemental Analysis: required C 59.3, H 4.68, N 8.13; found C 59.4, H 5.0, N 8.2.

NMR: δ 7.9-8.0, 7.7-7.78, 7.5-7.6, (2H, 1H & 2H, Ar), 7.2-7.4 (5H + solv. Ar), 6.5-6.7 (1H, broad NH), 5.15-5.2 (1H, m, CH ring), 4.1-4.5 (2H, m, NCH_2), 3.4-3.8 (2H, m, ring).

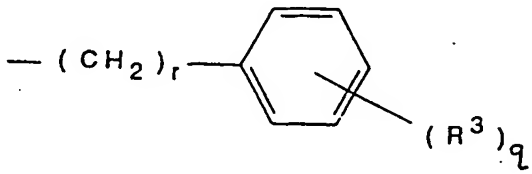
CLAIMS

1. A compound of formula I



I

wherein X is thio, sulphinyl or sulphonyl;
p is the integer 1 or 2;
each R^1, which may be the same or different, is selected from hydrogen, halogeno, carboxy, carbamoyl, cyano, hydroxy, amino, ureido, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, (2-5C)alkanoyl, (1-4C)alkoxycarbonyl, halogeno-(1-3C)alkyl, carboxy-(1-3C)alkyl, (1-4C)alkoxycarbonyl-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-(1-4C)alkylcarbamoyl-(1-3C)alkyl, N,N-di-[(1-4C)alkyl]carbamoyl-(1-3C)alkyl and (1-3C)alkylenedioxy;
R^2 is hydrogen; and
Y is hydrogen or (1-4C)alkyl or a group of the formula



wherein r is an integer from 0 to 2 and one of the methylene groups when r is the integer 1 or 2 may optionally bear one or two (1-4C)alkyl substituents;
q is the integer 1 or 2, and
each R^3, which may be the same or different, is selected from hydrogen, halogeno, cyano, hydroxy, amino, (1-4C)alkyl, (2-4C)alkenyl,

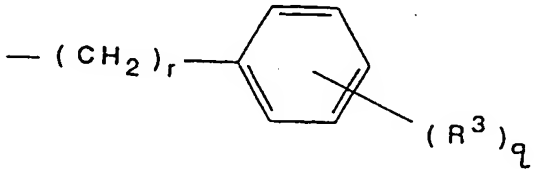
(2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-3C)alkyl and (1-3C)alkylenedioxy;
or a pharmaceutically-acceptable salt thereof.

2. A compound according to claim 1 wherein

(a) p is 1 or 2 and each R^1, which may be the same or different, is selected from hydrogen, fluoro, chloro, carboxy, carbamoyl, cyano, hydroxy, amino, ureido, methyl, ethyl, vinyl, allyl, ethynyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, acetamido, N-methylacetamido, acetyl, methoxycarbonyl, ethoxycarbonyl, trifluoromethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and methylenedioxy;

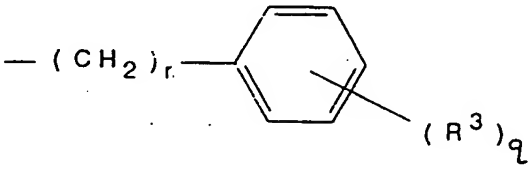
(b) Y is methyl, ethyl, propyl, isopropyl or butyl;

(c) Y is a group of the formula



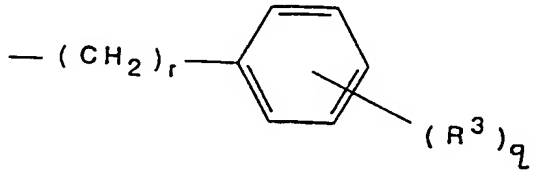
wherein r is 0 or 1, q is 1 or 2 and each R^3, which may be the same or different, is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl; or

(d) Y is a group of the formula



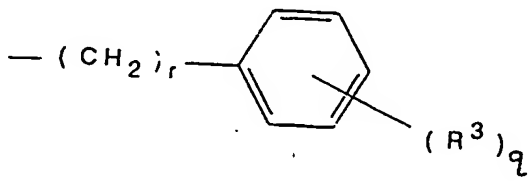
wherein r is 1 and the methylene group may optionally bear one or two substituents selected from methyl, ethyl, propyl and isopropyl, q is 1 or 2 and each R^3, which may be the same or different, is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

3. A compound according to claim 1 or 2 wherein
X is thio, sulphinyl or sulphonyl;
p is 1 or 2 and
each R^1, which may be the same or different, is selected from hydrogen, fluoro, chloro, carboxy, carbamoyl, cyano, hydroxy, amino, ureido, methyl, ethyl, methoxy, ethoxy, methylamino, dimethylamino, acetamido, N-methylacetamido, acetyl, methoxycarbonyl, ethoxycarbonyl, trifluoromethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and methylenedioxy;
R^2 is hydrogen; and
Y is methyl, ethyl, propyl, isopropyl or butyl, or
Y is a group of the formula



wherein r is 0 or 1, q is 1 or 2 and
each R^3, which may be the same or different, is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

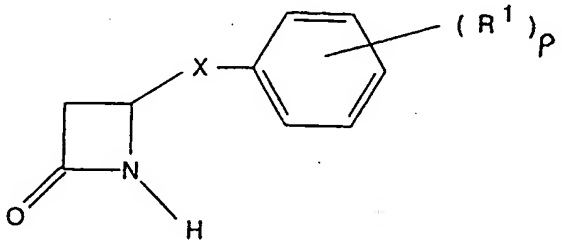
4. A compound according to any preceding claim wherein
X is thio;
p is 1 and
R^1 is selected from hydrogen, fluoro, chloro, carboxy, carbamoyl, methyl, methoxy, methoxycarbonyl, ethoxycarbonyl, trifluoromethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl and carbamoylmethyl;
R^2 is hydrogen; and
Y is a group of the formula



wherein R is 1, q is 1 and
R^3 is selected from hydrogen, fluoro, chloro, methyl, ethyl, methoxy and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

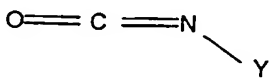
5. The compound
1-(N-benzylcarbamoyl)-4-(phenylthio)azetidin-2-one;
or a pharmaceutically-acceptable salt thereof.

6. A process for the preparation of a compound of Formula I and salts thereof comprising
(a) coupling of an azetidin-2-one of the formula II



II

and an isocyanate of the formula III



III

and optionally converting a compound of Formula I thus obtained into a salt thereof;
(b) a process for the preparation of compounds of Formula I wherein X is a sulphinyl or sulphonyl group in which the process comprises oxidation of a compound of the formula I wherein X is a thio group and optionally converting a compound of Formula I thus obtained into a salt thereof.
7. A pharmaceutical composition which comprises an amide derivative of Formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

8. A compound of Formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

9. A method of treating a disease or medical condition mediated alone or in part by tumour necrosis factor (TNF) which comprises administering to a warm-blooded animal requiring such treatment an effective amount of a pharmaceutical composition as defined in claim 7.

10. Use of a compound of Formula I as defined in claim 1 in production of a medicament for use in a TNF mediated disease or medical condition.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/GB 94/01466

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D205/09 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 337 549 (MERCK & CO., INC.) 18 October 1989 cited in the application see page 22, line 26 - line 27; claims ---	1-10
A	EP,A,0 481 671 (MERCK & CO., INC.) 22 April 1992 cited in the application see claims ---	1-10
A	EP,A,0 199 630 (MERCK & CO., INC.) 29 October 1986 cited in the application see claims -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 1994	26.09.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB94/01466

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK : ALTHOUGH CLAIMS 8,9 ARE DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COUPOUND/COMPOSITION.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ERNATIONAL SEARCH REPORT

Information on patent family members

Interna... ...plication No
PCT/GB 94/01466

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0337549	18-10-89	AU-A-	1858292	10-09-92
		AU-A-	3263089	12-10-89
		JP-A-	2006471	10-01-90
		US-A-	5229381	20-07-93
EP-A-0481671	22-04-92	AU-B-	648345	21-04-94
		AU-A-	8583391	19-12-91
		JP-A-	5132458	28-05-93
		US-A-	5229381	20-07-93
EP-A-0199630	29-10-86	US-A-	4680391	14-07-87
		JP-A-	61289074	19-12-86
		US-A-	5229381	20-07-93
		US-A-	5229510	20-07-93